

REMARKS

New claims 39-41 are pending in the application. Former claims 1-38 have been deleted without prejudice. New claims 39-41 have been added. New claims 39-41 are encompassing the subject matter claimed in former claim 3, restricted to specific oligonucleotides (SEQ ID NO: 22, REP 2006 and SEQ ID NO: 24) which are exemplified in the description. No new matter has been hereby introduced.

Claim rejections - 35 U.S.C. § 112

Claims 3-32 have been rejected under 35 U.S.C. § 112, second paragraph, as indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner notes that the statement "principally by a non-sequence complementary mode of action" in claim 3 is unclear. More specifically, it is unclear what % of this mode of action is required to be "principally", and how this is determined. Further, the Examiner states that the statement "said composition is approved for use in humans against HBV" in claim 3 is also indefinite because it is not clear who approved said composition. In this regard, the Applicants wish to respectfully submit that former claims 3-32 have been cancelled and that the unclear expressions identified by the Examiner are not recited in new claims 39-41 submitted herewith. In view of the amendments presented hereinabove, reconsideration and withdrawal of the Examiner's rejection are earnestly solicited.

Claims 3-32 have been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. The Examiner specifically states that the only structural limitation to the claimed oligonucleotides is the minimal length, and thus claims 3-32 encompass all oligonucleotides that are more than 10 nucleotides in length. The possible variations are indefinite to such oligonucleotides longer than 10 nucleotides. The Examiner argues that the specification only provides a description for 36 oligonucleotides, which do not constitute a representative number of

species for such a broad genus. Consequently, the Examiner is of the opinion that the claims may recite some functional characteristics, but lack written description because there is no disclosure of a correlation between function and structure of the oligonucleotides in the examples in the specification. In this regard, the Applicants respectfully submit that former claims 3-32 have been deleted and that new claims 39-41 have been added. These new claims are restricted to the oligonucleotides consisting of SEQ ID NO: 22, SEQ ID NO: 24 and REP 2006 for treating HBV infections. The Applicants also submit that results are disclosed in the application (see Example 8) and were presented in the Declaration of Dr. Jean-Marc Juteau submitted November 1, 2006, demonstrating the anti-HBV activity of REP 2006 and of SEQ ID NO: 22. Further, enclosed herewith is a Declaration from Dr. Jean-Marc Juteau disclosing the *in vivo* efficacy of REP 2006, SEQ ID NO: 22 and SEQ ID NO: 24 to inhibit HBV infection in a recognized animal model. It is thus submitted that the claims now on file are directed to specific oligonucleotides, having specific structure limitation. Consequently, in view of the arguments and amendments presented hereinabove, reconsideration and withdrawal of the Examiner's rejection are earnestly solicited.

Claims 3-32 have been further rejected as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to practice the present invention. The Examiner states that the claims recite the limitation that "the antiviral activity of said oligonucleotide occurs principally by a non-sequence complementary mode of action". The Examiner is of the opinion that the specification has not disclosed any structures of oligonucleotides whose antiviral activity "occurs principally by a non-sequence complementary mode of action", nor a correlation between the structures and "action mode" of the oligonucleotides. The Examiner further argues that, in order to use or make the instant pharmaceutical composition, one skilled in the art would have to make and test indefinite oligonucleotides that are more than 10 nucleotides in length to determine which oligonucleotides meet the functional limitation of antiviral activity and the "action mode" limitation of "acting by a non-sequence complementary mode of action". The Examiner believes that the Applicant has demonstrated that some random oligonucleotides can inhibit DHBV in cell culture; however, and alleges that the specification has not disclosed that such

oligonucleotides can inhibit HBV *in vivo*. The Examiner further mentions that the Declaration filed November 2, 2006, wherein it was reported that REP 2006, REP 2004 and REP 2031 (SEQ ID NO: 22) can inhibit DHBV infection in primary duck hepatocytes and cell lines, has been fully considered and found unpersuasive. More specifically, the Examiner feels that the examples disclosed in the Declaration are not representative of the whole scope of the claimed subject matter.

In this regard, the Applicants submit that former claims 3-32 have been deleted from the present application. New claims 39-41 have been added, wherein these new claims are restricted to specific oligonucleotides consisting of SEQ ID NO: 22, SEQ ID NO: 24 and REP 2006. These specific oligonucleotides all have phosphorothioated linkages. Further, regarding the mode of action, the Applicants wish to point out that the present application teaches oligonucleotides having a non-sequence complementary mode of action. For example, with randomer oligonucleotides (as for example REP 2006) as taught in the present description, due to the nature of the preparation used to produce them, a sequence complementary mode of action cannot occur. On page 34 of the present description, it is clearly disclosed that for a randomer oligonucleotide of 40 bases in length, any particular sequence in the population would theoretically represent only $1/4^{40}$ or 8.27×10^{-25} of the total fraction. Given that 1 mole = 6.022×10^{23} molecules, and the fact that the largest synthesis is currently done on a 15 micromole scale, all possible sequences will not be present. Also, there is most probably only one copy of each sequence. Consequently, by its inherent properties, the mode of action of these oligonucleotides is sequence independent, or occurring by a non-sequence complementary mode of action, and does not require complementarity to the nucleic acid sequence of a gene. Similarly, by the nature of the sequence of SEQ ID NOs: 22 and 24, these sequences are not complementary to the nucleic acid sequence of a gene of the HBV virus, and thus the anti-HBV activity of these oligonucleotides is occurring by a non-sequence complementary mode of action.

The Applicants also submit that results demonstrating the anti-HBV activity of REP 2006 and of SEQ ID NO: 22 are disclosed in the application (see Example 8). In addition, as acknowledged by the Examiner, further results were presented in Dr. Jean-Marc Juteau's Declaration submitted November 1, 2006. Enclosed herewith is a Declaration from Dr. Jean-Marc Juteau

disclosing the *in vivo* efficacy of REP 2006, SEQ ID NO: 22 and SEQ ID NO: 24 to inhibit HBV infection in an animal model. The infection of ducks with the duck HBV is considered to be a surrogate animal model to closely approximate the infection of humans with HBV. The duck HBV model closely mimics the liver infection of human HBV infection. The duck HBV *in vivo* model responds to treatment with antiviral drugs and is considered a good model for *in vivo* activity testing (see enclosed references of Funk *et al.*, Foster *et al.* and Seignères *et al.*).

The Applicants wish to remind the Examiner that, as set out in the *Manual of Patent Examining Procedures* (MPEP, section 2107.03), the office personnel should not impose on an Applicant the unnecessary burden of providing evidence from human clinical trials, i.e. no decision exists in law that requires an Applicant to provide data from human clinical trials to establish utility for an invention relating to the treatment of human disorders. It is clearly stated that when there is reasonable correlation between the activity in question and the asserted utility, there is no basis in the statutes or decisions for requiring any more conclusive evidence of operativeness. An Applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such utility is asserted. Instead, the Courts have repeatedly held that all that is required is a reasonable correlation between the activity and the asserted use. If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays or from testing on an animal or a combination is invariably sufficient to establish therapeutic or pharmacological utility of a compound, composition or process.

Consequently, the Applicants clearly demonstrated a correlation of the anti-HBV activity of the specific oligonucleotides as now claimed *in vitro* and their efficacy *in vivo*, and thus a person skilled in the art is able to fully predict possible results of the clinical benefit of the claimed pharmaceutical composition only based on these results. Thus, one skilled in the art will accept that testing the efficacy of a compound infection of ducks with the duck HBV is reasonably predictive of utility in humans, and evidence from such tests should be considered sufficient to support the

credibility of the asserted utility. In view of the arguments and amendments presented hereinabove, reconsideration and withdrawal of the Examiner's rejection are earnestly solicited.

Claim rejections - 35 U.S.C. § 102

Claims 3, 12, 14, 15, 17, 18, 21, 25, 26 and 28-32 have been rejected under 35 U.S.C. 102(b) as anticipated by Pan *et al.* In this regard, the Applicants submit that former claims 3, 12, 14, 15, 17, 18, 21, 25, 26 and 28-32 have been deleted from the present application. Further, the reference of Pan *et al.* only teaches the isolation of specific sequences or RNA that binds and neutralizes the RSV virus. These sequences are isolated from a large pool of random sequences by cycles of in vitro selection. It is stated in Pan *et al.*, on page 1 (in the introductory part of the reference) that "*Here we use RSV to demonstrate that without knowledge of the structures of viral proteins, antiviral RNAs and RNA analogs can be isolated systematically and effectively from a large pool of random sequences, first by using intact viral particles to select from the sequence pool the RNAs and RNA analogs that bind specifically to virus, and subsequently by screening the selected molecules for the ability to neutralize the virus*". As disclosed in Fig. 4B of Pan *et al.*, the selection cycles allow the authors to identify very specific sequences. In Pan *et al.*, there is neither disclosure nor suggestion of oligonucleotides, much less of REP 2006, SEQ ID NO: 22 and SEQ ID NO: 24, having antiviral activity occurring by a non-sequence complementary mode of action and, more specifically, antiviral activity against HBV. Consequently, it is believed that the document of Pan *et al.* does not anticipate or render obvious the subject matter claimed in new claims 39-41.

Claims 3-13 and 16-32 have been rejected under 35 U.S.C 102(e) as anticipated by Davis (U.S. Patent No. 6,406,705). The Applicants wish to reiterate that former claims 3-13 and 16-32 have been deleted from the present application. Further, the document of Davis teaches that immunostimulatory oligonucleotides having at least one unmethylated CpG dinucleotides can be used for induction of cellular immunity against HBV. Davis only teaches products utilizing a synergistic combination of oligonucleotides having at least one unmethylated CpG dinucleotide and a non-nucleic acid adjuvant. Davis *et al.* neither teaches nor suggests that oligonucleotides can

possess antiviral activity occurring by a non-complementary mode of action. Thus, in order for Davis' product to be effective, the CpG oligonucleotide is administered with a non-nucleic acid adjuvant which differs from the present application wherein the antiviral activity is conferred by the oligonucleotide itself. Contrary to the Examiner's belief that Davis teaches the use of a CpG oligonucleotide as an adjuvant alone or in combination with other adjuvants, the Applicants submit that Davis teaches away from this statement since it emphasizes the synergistic effect of injecting a CpG oligonucleotide with an adjuvant. On the contrary, as claimed in claim 1 in Davis, it is clearly stated in column 1, lines 15-19 that: *"The present invention relates generally to adjuvants, and in particular to methods and products utilizing a synergistic combination of oligonucleotides having at least one unmethylated CpG dinucleotide (CpG ODN) and a non-nucleic acid adjuvant."* Consequently, nowhere is there teaching nor suggestion of oligonucleotides in Davis, more specifically of REP 2006, SEQ ID NO: 22 and SEQ ID NO: 24, having anti-HBV activity occurring by a non-sequence complementary mode of action. Furthermore, the oligonucleotides taught in the present application and claimed in new claims 39-41 do not need to possess at least one unmethylated CpG dinucleotide to have anti-viral activity. It is thus believed that the document of Davis does not anticipate or render obvious the subject matter claimed in new claims 39-41.

Double Patenting

Claims 3-32 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 and 18-26 of copending Application No. 10/661,403. In addition, claims 3-32 have also been rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 22-51 of copending Application No. 10/661,402, over claims 3-32 of copending Application No. 10/661,415, and over claims 23-52 of copending Application No. 10/969,812. In this regard, Applicants respectfully submit that former claims 3-32 have been deleted from the present application. However, in anticipation of a new rejection of claims 39-41 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 and 18-26 of copending Application No. 10/661,403; over claims 22-51 of copending Application No. 10/661,402; over claims 3-32 of

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copending Application No. 10/661,415; and over claims 23-52 of copending Application No. 10/969,812, the Applicants submit that this rejection should be moot in light of the Terminal Disclaimer under 37 C.F.R. §1.321 enclosed herewith.

It is submitted, therefore, that the claims are in condition for allowance. Reconsideration of the Examiner's rejections is respectfully requested. Allowance of claims 39-41 at an early date is solicited.

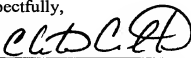
No additional fees are believed to be necessitated by this amendment. Should this be in error, authorization is hereby given to charge Deposit Account No. 19-5113 for any underpayment or to credit any overpayment.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully,

Date: July 23, 2007

By: _____



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Enc.: Declaration
CV of Dr. Juteau
Petition for extension of time
Terminal Disclaimer
Funk *et al.*, Foster *et al.* and Seignères *et al.*